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Gefitinib Combined with Cetuximab for the Treatment of Lung Adenocarcinoma Harboring the *EGFR*–Intergenic Region (*SEC61G*) Fusion and *EGFR* Amplification

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Key Words. *EGFR* fusion • *EGFR* amplification • Lung adenocarcinoma

Abstract

EGFR fusions are rare genomic events in non-small cell lung cancer (NSCLC), and a total of nine types have been previously reported in lung adenocarcinoma: *EGFR-RAD51*, *EGFR-PURB*, *EGFR-ANXA2*, *EGFR-ZNF713*, *EGFR-YAP1*, *USP42-EGFR*, *EGFR-SEPTIN14*, *EGFR-TNS3*, and *EGFR-ZCCHC6*. *EGFR* fusion mutations combined with *EGFR* amplification are even rarer in NSCLC. The *EGFR*–intergenic region (IGR) fusion mutation is unreported, and thus, there are no studies targeting this fusion together with *EGFR* amplification in lung adenocarcinoma. Our brief study provides clinical evidence that combined targeted therapy with gefitinib and cetuximab could result in a significant antitumor response in patients with the *EGFR*-IGR fusion and *EGFR* amplification. ***The Oncologist*** 2021;26:e1898–e1902

Key Points

- *EGFR* fusion mutations are rare, and *EGFR* fusion mutations combined with *EGFR* amplification are even rarer in non-small cell lung cancer (NSCLC). To the authors' knowledge, there is no previous report on the coexistence of the *EGFR*–intergenic region (IGR) fusion and *EGFR* amplification.
- This is the first report of a patient with NSCLC with the *EGFR*-IGR fusion and *EGFR* amplification who achieved a significant antitumor response from treatment with gefitinib combined with cetuximab.

Patient Story

A 68-year-old man with an approximately 100-pack-year smoking history complained of chest pain and was admitted to our hospital on September 12, 2020. Thoracic computed tomography (CT) and positron emission tomography (PET)–CT scans showed a 2.6-cm right upper lung mass and metastatic carcinoma of the left fourth rib (Fig. 1A; Fig. 2A). A CT-guided biopsy of the pulmonary lesion showed that the mass was a lung adenocarcinoma, and the patient was diagnosed with lung adenocarcinoma (cT1bN0 M1b stage IVA) with solitary bone metastasis. A biopsy tissue sample was obtained for next-generation sequencing (NGS) using a panel of 14 cancer-related genes (Geneseeq, Nanjing, China) on September 24, 2020.

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The *EGFR*–intergenic region (IGR) (*SEC61G*) fusion (the mutation abundance was 79.8%; Fig. 3) and *EGFR* amplification (copy number: 5.6) were detected. The breakpoint positions of *EGFR*-IGR were near *EGFR* 7p11.2, which includes *EGFR* exons 1–25 (1,005 amino acids) and 32 amino acids downstream of *SEC61G*.

Limited evidence suggests that patients with *EGFR-RAD51* [1–4], *EGFR-PURB* [1], and *EGFR-SEPTIN14* [5] mutations exhibit a marked tumor response to EGFR tyrosine kinase inhibitor (TKI) therapies [1–5]. Herein, we report a case of lung adenocarcinoma with a novel *EGFR* fusion type (*EGFR*-IGR) as well as *EGFR* amplification, which added to the complexity of the treatment of this patient.

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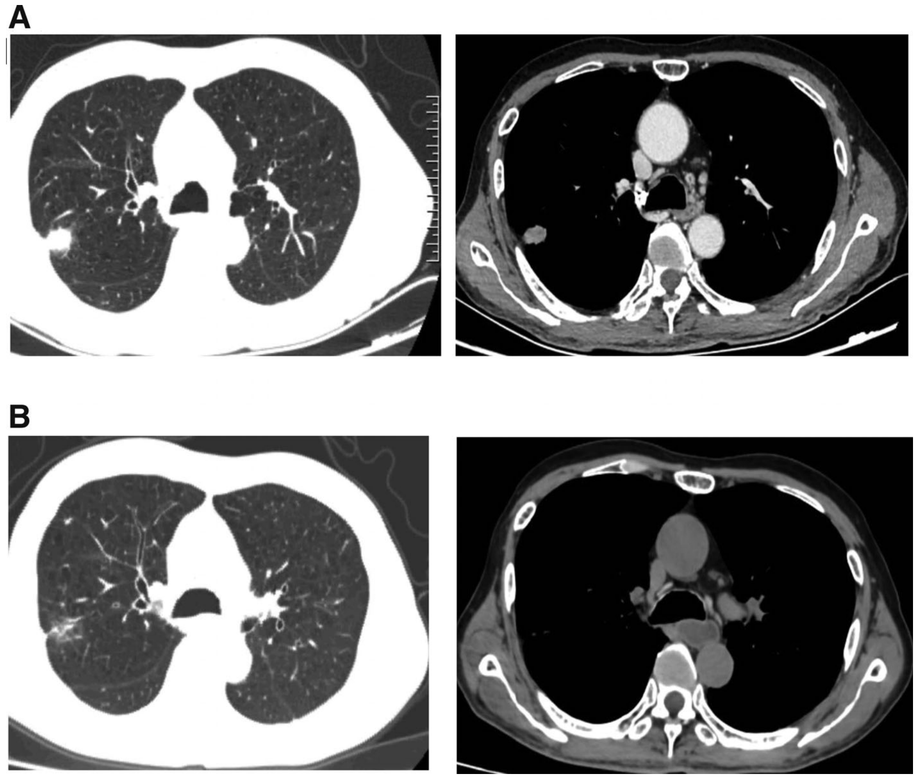

Figure 1. **(A):** Computed tomography (CT) scan before gefitinib and cetuximab treatment. **(B):** CT scan showing a partial response after 2 months of gefitinib and cetuximab treatment.

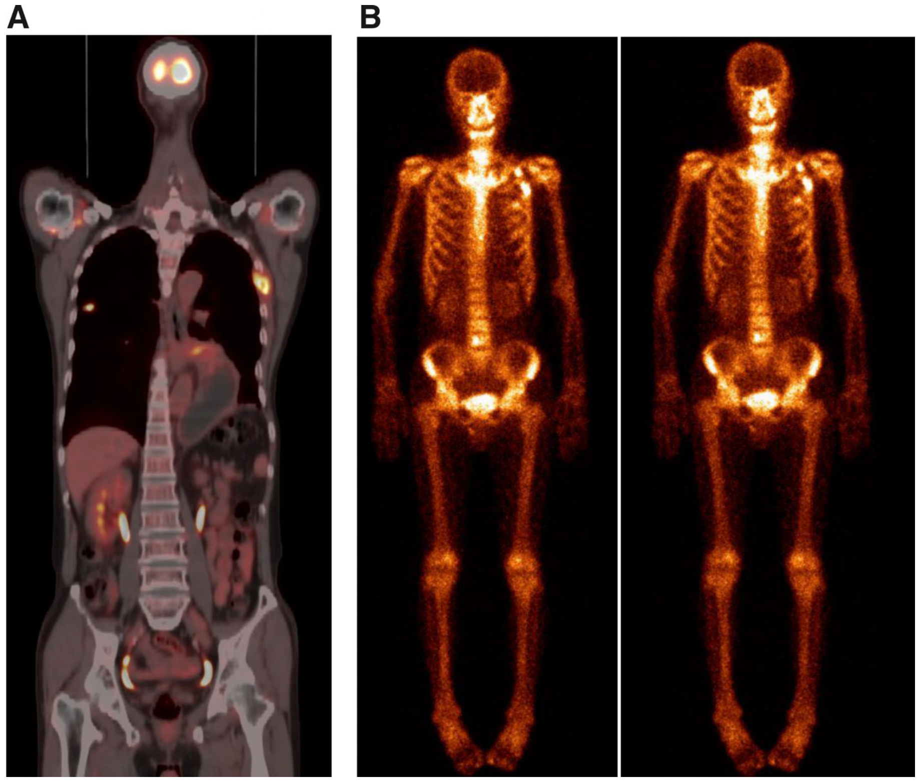

Figure 2. The foci of the left fourth rib turned out to be a fracture 2 months after diagnosis. **(A):** Positron emission tomography–computed tomography scan showed a right upper lung mass and metastatic foci of the left fourth rib. **(B):** The foci showed no response to treatment from two consecutive (November 2, 2020, and December 3, 2020) bone scintigraphies (and turned out to be benign, as revealed by bone biopsy).

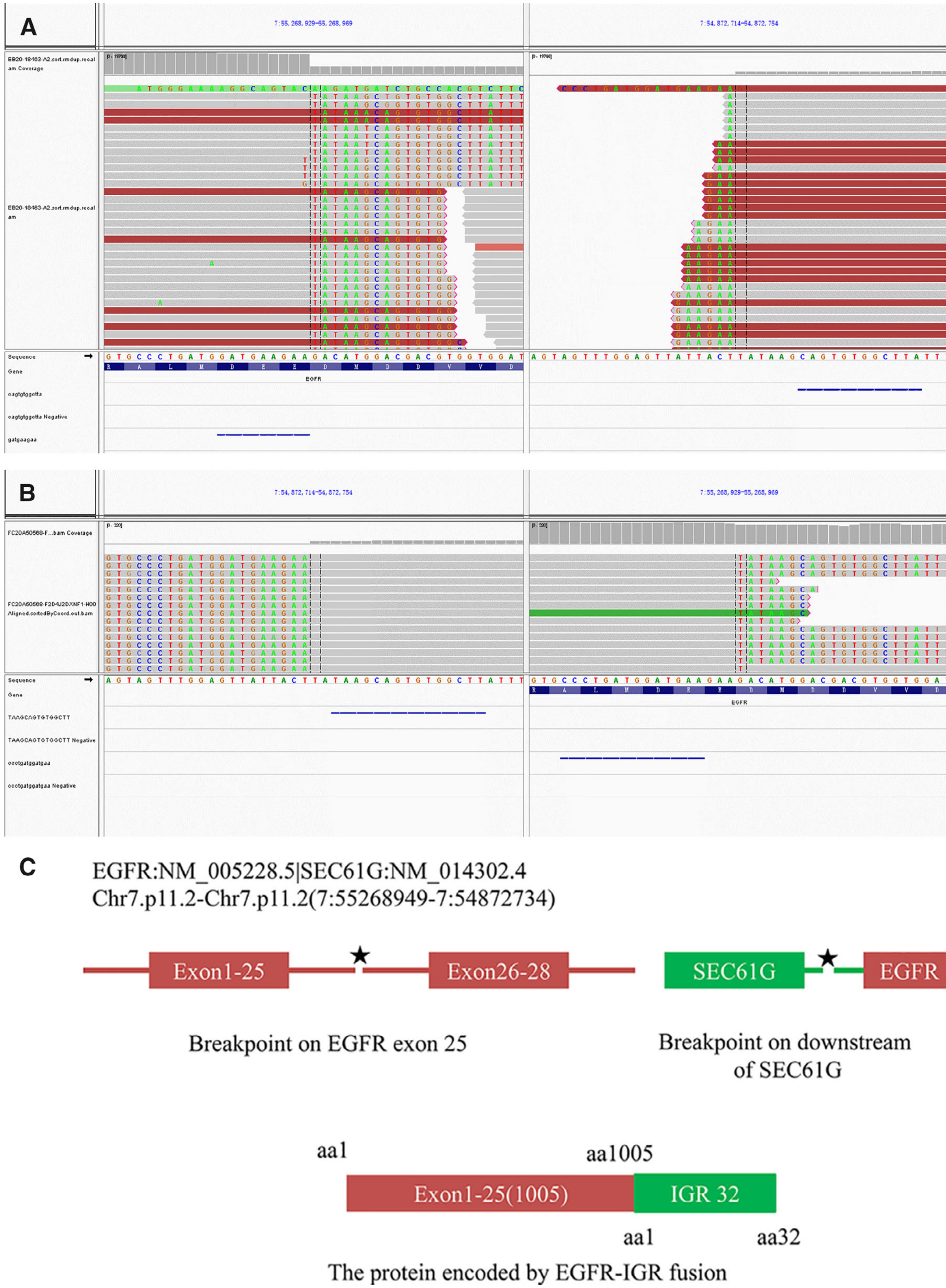

Figure 3. (A): Integrative Genomics Viewer snapshot of *EGFR*–intergenic region (IGR) fusion (DNA analysis). **(B):** Integrative Genomics Viewer snapshot of *EGFR*-IGR (RNA analysis). **(C):** Schematic representation of the *EGFR*-IGR fusion protein domain structure.

EGFR contains several autophosphorylation sites in the C-terminal tail of the receptor that positively regulate the transforming activity of EGFR by mediating downstream proliferative signaling. Previous studies have shown that autophosphorylation sites in the regulatory domain, which serve as docking sites for signaling adaptor proteins, are lacking in most *EGFR* fusion mutations [1]. In our case, the breakpoint positions of *EGFR*-IGR were near *EGFR* 7p11.2, which includes *EGFR* exons 1–25 (1,005 amino acids) and 32 amino acids downstream of *SEC61G*. That is, the kinase domain of *EGFR*-IGR contains tyrosine 845, tyrosine 920, and tyrosine 992 phosphorylation sites, which have been confirmed to be oncogenic [6]. Studies have shown that several types of *EGFR* fusions can be therapeutically targeted with EGFR TKIs. Thus, we assumed that our patient might benefit from EGFR TKIs.

EGFR overexpression leads to asymmetric dimer formation, increased downstream signaling activation, and consequent oncogenicity. However, the evidence supporting the application of this mutation as a biomarker for EGFR TKI therapy response is weak. Although studies have demonstrated that *EGFR* amplification is a biomarker for the response to EGFR TKI therapy in patients with advanced non-small cell lung cancer (NSCLC) [7], the predictive value of *EGFR* amplification may be driven by coexisting *EGFR* mutations [8]. Additionally, *EGFR* amplification has been shown to be one of the most common resistance mechanisms in patients undergoing treatment with third-generation EGFR TKIs [9].

The efficacy of EGFR monoclonal antibodies (mAbs) has been evaluated in lung cancer for a long time, and the findings are highly controversial. Fortunately, the EGFR expression level or the *EGFR* gene copy number may be a predictive factor of the clinical benefit of the addition of cetuximab to the chemotherapy regimen [10–12]. As our patient exhibited high EGFR expression and *EGFR* amplification, we predicted that he might benefit from EGFR mAbs.

However, no investigation has focused on the *EGFR*-IGR fusion mutation combined with *EGFR* amplification, leaving the optimal therapy unclear. Recently, the combination of an EGFR TKI (afatinib) with cetuximab did not improve outcomes in previously untreated *EGFR*-mutant NSCLC [13]. We were interested in searching for a therapeutic regimen for our unique patient, and we sought to determine the effectiveness of EGFR TKIs combined with cetuximab against the *EGFR*-IGR fusion combined with *EGFR* amplification.

Case Report

After discussing the patient's case, the lung cancer multidisciplinary team (MDT) recommended treatment with gefitinib (250 mg every day) and cetuximab (500 mg/m^2 every 2 weeks) on October 1, 2020. The risks and benefits of the combination of gefitinib with cetuximab treatment were fully explained to the patient. Informed consent was obtained from the patient, and this study was approved by the Zhengzhou University Institutional Review Board. After 2 months, a chest CT scan showed a decrease in tumor size (Fig. 1B). In particular, the metastatic foci of the left fourth rib diagnosed from PET-CT (Fig. 2A) turned out to be a fracture, as shown by two consecutive bone scintigraphies (Fig. 2B) and a bone biopsy. According to RECIST guidelines, the patient was considered to have a partial response to gefitinib combined with cetuximab. The side effect of the treatment was third-degree facial acne.

Another discussion with the lung cancer MDT after 2 months of treatment led to the conclusion that the patient should undergo surgical treatment. After adequate preoperative preparation, a right upper lobectomy with mediastinal lymphadenectomy was performed. The final pathology report revealed a 1.3-cm pyT1bN0 adenocarcinoma. Another NGS analysis of the tumor was conducted. Interestingly, the results illustrated that the former *EGFR*-IGR fusion mutation and *EGFR* amplification disappeared, and no drug-resistance–conferring mutations appeared.

Herein, we provide the first report of a patient with NSCLC with the *EGFR*-IGR fusion and *EGFR* amplification who achieved a significant antitumor response from treatment with gefitinib combined with cetuximab. In the future, we intend to explore fundamental research on such rare mutations in terms of the mechanism of tumorigenesis.

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Glossary of Genomic Terms and Nomenclature

EGFR: epidermal growth factor receptor

IGR: intergenic region

Author Contributions

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Disclosures

The authors indicated no financial relationships.

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